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Interactions of β-adrenoceptor antagonists and thyroid hormones in the control of heart rate in the dog

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1 Propranolol, sotalol and nadolol have been infused into conscious dogs, and doses at which the three drugs are equipotent as β-adrenoceptor antagonists determined.

2 In euthyroid dogs, sotalol was more effective at lowering heart-rate than an equivalent dose of propranolol, while an equivalent dose of nadolol was without effect.

3 Hyperthyroidism potentiated the lowering of heart-rate by sotalol, but inhibited that by propranolol.

4 The effect of sotalol on heart-rate was correlated with its prolongation of the Q-T interval of the ECG. That of propranolol was correlated with its prolongation of the P-R interval. Nadolol did not affect P-R interval or Q-T interval except at relatively high dosage.

5 We conclude that the tachycardia of hyperthyroidism is not affected by blockade of β-adrenoceptors and therefore that it is not mediated by adrenergic mechanisms. The effectiveness of propranolol and sotalol in lowering heart-rate must be due to actions peculiar to those drugs, and not to β-adrenoceptor antagonism.

Introduction

Propranolol, in adequate doses, lowers the high heart-rates of thyrotoxic patients (Shanks *et al.*, 1969). Binding studies with radio-labelled β-adrenoceptor ligands have shown increased binding to membranes from hyperthyroid, in comparison with those from euthyroid animals. From this evidence it has been argued that the tachycardia of thyrotoxicosis is at least partly mediated by increased sympathetic activity or increased responsiveness to catecholamines (Klein & Levey, 1984).

This argument is weakened by two observations: (i) studies on hyperthyroid patients have failed to show increased sympathetic responsiveness (Forfar *et al.*, 1982) and (ii) pharmacological studies on isolated hearts from hyperthyroid animals have not shown enhanced responses to β-adrenoceptor antagonists (Rub *et al.*, 1981).

Furthermore, the reduction of heart-rate in thyrotoxic patients by propranolol could be due to actions other than β-adrenoceptor antagonism, such as (a) direct actions on myocardial ion-channels, or (b) inhibition of the conversion of thyroxine (T4) to triiodothyronine (T3) in the tissues (Heyma *et al.*, 1980).

We have compared the effects on heart-rate of three β-adrenoceptor antagonists, propranolol, sotalol, and nadolol, in conscious dogs before and after treatment with T3 and with carbimazole. We have also measured the components of the electrocardiogram associated with conduction and with ventricular depolarization, and related changes in these to actions peculiar to individual drugs and independent of adrenoceptor antagonism.

A preliminary account of this work has been published (Allely & Ungar, 1984).

Methods

Male foxhounds, weighing 22–33 kg, were trained to lie still on their sides in a basket while the electrocardiogram (ECG) was recorded from metal plate surface electrodes strapped to their legs. The recording was made on a Devices pen recorder, with a paper speed of 100 mm s^{-1}. The ECG lead was chosen which gave the clearest measurement of P-R and Q-T intervals. Drugs or saline solution were infused through a 21 gauge butterfly needle in a radial vein.

Thyroid state

After studies in the normal state, each dog was given carbimazole (1 mg kg^{-1} twice daily by mouth) for 3 weeks before and during the period of study in order to

depress thyroid function. After a recovery period of 4 weeks, the dogs were made hyperthyroid by the administration of T3 ($3.3\,mg\,kg^{-1}$ twice daily by mouth), again for 3 weeks before and during the second study period.

The thyroid state was monitored at each stage of the experiment by the estimation of T3 and T4 in venous plasma by radioimmunoassay. Blood samples were taken before the morning dose of drug.

Potencies of adrenoceptor antagonists

In each dog we estimated the relative doses of propranolol, sotalol and nadolol that were equipotent in raising the dose of isoprenaline needed to evoke a given chronotropic response. Logarithmic dose-response curves for isoprenaline were constructed before and after the infusion of each antagonist on two occasions. A consistent parallel shift was obtained in each case, and this enabled us to predict the isoprenaline dose-ratio (IDR) for intermediate doses of the drugs. We were thus able to compare actions of the drugs other than adrenoceptor antagonism at doses giving equal IDR.

Experimental protocol

Experiments were carried out on 4 dogs. Each of the three antagonist drugs was infused 6 times into each dog, twice during each thyroid state. At least 3 days were allowed for recovery after each infusion. At the start of each experiment, saline solution was infused and the ECG recorded, while the dog settled to a constant heart-rate. Propranolol, sotalol or nadolol, in random order, was then infused at a constant rate for 40 min. The total dose of each drug was calculated to give a predicted IDR above 30.

Analysis of results

The ECG record was analysed for sets of 10 successive beats at 5 min intervals. The mean R–R, P–R, and Q–T intervals for each set of beats were determined. A regression analysis of heart-rate, P–R interval, and Q–T interval on dose of drug delivered was performed for each antagonist drug infusion. Responses to the three drugs were interpolated for doses giving equal predicted IDR. Differences between these responses were taken to reflect actions not mediated by β-adrenoceptors.

The statistical significance of the differences between treatments was assessed by the Wilcoxon signed rank test.

Drugs

The following drugs (sources in parentheses) were used: carbimazole (Nicholas); triiodothyronine (Sigma); propranolol hydrochloride (I.C.I.); sotalol hydrochloride (Bristol Myers); nadolol hydrochloride (Squibb).

Results

Thyroid state

The mean venous plasma concentrations of T3 and T4 after 4 weeks of each phase of the study are shown in Figure 1. T4 was significantly depressed by carbimazole and also by T3 treatment ($P < 0.05$). T3 was not significantly depressed by carbimazole, but was raised more than 4 fold by T3 administration ($P < 0.001$).

During carbimazole treatment all the dogs became sluggish in their behaviour and all gained weight (0.6–1.3 kg), but they showed no significant change in heart-rate. During T3 treatment they all became restless and lost weight (2.1–3.7 kg), and their mean heart-rates rose from 89 to 136 ($P < 0.05$).

Relative potencies of antagonists

Isoprenaline, in intravenous doses between 10 and $100\,ng\,kg^{-1}$ evoked increases in heart-rate that gave consistant logarithmic dose-response curves. All three antagonists gave parallel shifts in the isoprenaline-response curves up to an IDR of 50. For higher doses of nadolol the block became unsurmountable, with a

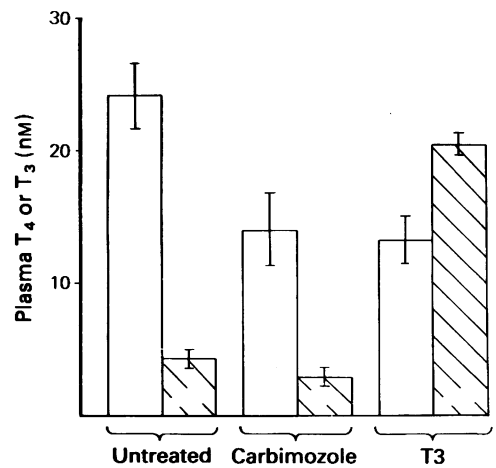

Figure 1 Mean concentrations of T4 (open columns) and T3 (hatched columns) in venous plasma from 4 dogs while untreated, after 3 weeks treatment with carbimazole ($1\,mg\,kg^{-1}$ twice daily), and after 3 weeks treatment with T3 ($3.3\,mg\,kg^{-1}$ twice daily). Vertical bars represent s.e.mean.

Table 1 Mean values of heart-rate and ECG intervals in the three phases of the study, before the administration of β-adrenoceptor antagonists

Variable	*Hypothyroid*	*Euthyroid*	*Hyperthyroid*
Heart-rate (beats/min)	88 ± 7	92 ± 11	135 ± 9*
P–R interval (ms)	117 ± 3	114 ± 3	106 ± 3
Q–T interval (ms)	216 ± 3	221 ± 9	235 ± 9*

The standard error for each mean is given.
*Significantly different from euthyroid ($P < 0.05$)

reduced maximum response to isoprenaline. Responses to isoprenaline in the presence and absence of each of the antagonists are illustrated in Figure 2. The doses of the antagonists giving equal IDR were in the ratio: propranolol:sotalol:nadolol = 1:9:0.03.

Actions on heart-rate

Table 1 shows the resting values for the three phases of the study, and Figure 3 shows the changes evoked by the three antagonists, all at doses giving an IDR of 30. These doses were: propranolol 0.39 mg kg^{-1}; sotalol 3.6 mg kg^{-1}; nadolol 0.011 mg kg^{-1}.

Nadolol had no significant effect in all three thyroid states. The reduction in heart rate given by propranolol was significantly smaller in T3-treated than in the untreated or carbimazole-treated state ($P < 0.05$). The reduction in heart rate given by sotalol, on the other hand, while greater than that for propranolol in the untreated state was significantly potentiated by T3 ($P < 0.05$).

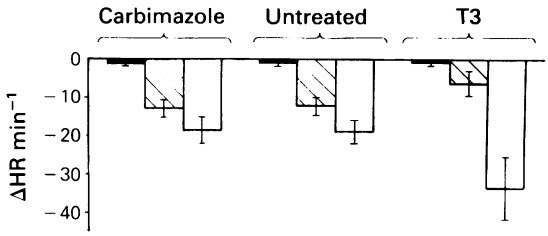

Figure 3 Mean changes in heart-rate evoked by the infusion of nadolol (solid columns), propranolol (hatched columns), and sotalol (open columns), all at doses giving IDR = 30. Results of duplicate experiments on 4 dogs untreated, during carbimazole-treatment, and during T3-treatment. Vertical bars represent s.e.mean.

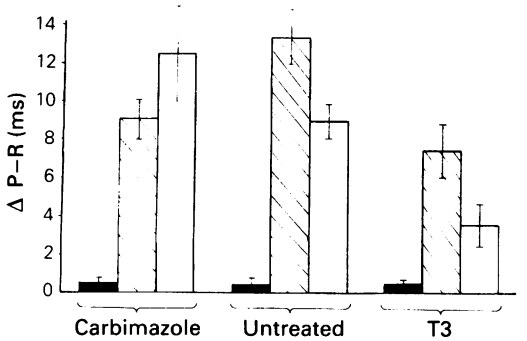

Figure 4 Mean changes in P–R interval evoked by the infusion of nadolol (solid columns), propranolol (hatched columns), and sotalol (open columns), all at doses giving IDR = 30. Results of duplicate experiments on 4 dogs untreated, during carbimazole treatment, and during T3 treatment. Vertical bars represent s.e.mean.

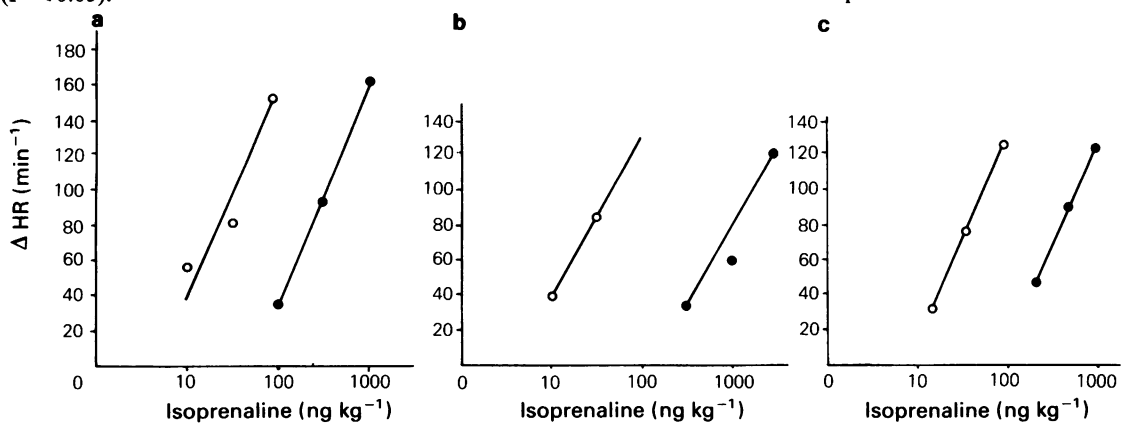

Figure 2 Heart rate responses to intravenous injection of isoprenaline before (○) and after (●) the infusion of (a) sotalol hydrochloride (1.25 mg kg^{-1}), (b) propranolol hydrochloride (500 μg kg^{-1}) and (c) nadolol hydrochloride (3.64 μg kg^{-1}). Each symbol represents the mean of duplicate experiments in 4 dogs. The lines represent least squares fit for the pooled data.

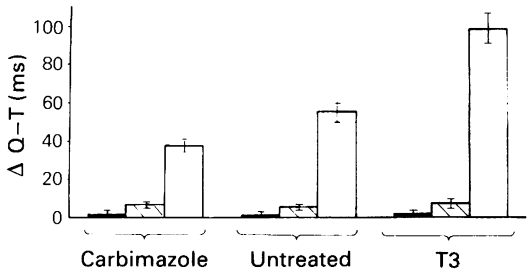

Figure 5 Mean changes in Q–T interval evoked by the infusion of nadolol (solid columns), propranolol (hatched columns), and sotalol (open columns), all at doses giving IDR = 30. Results of duplicate experiments on 4 dogs untreated, during carbimazole-treatment, and during T3-treatment. Vertical bars represent s.e.mean.

Actions on P–R interval

Figure 4 shows the changes evoked by the three antagonists, at the same doses as in the previous section, from the resting values shown in Table 1.

Nadolol again was without significant effect throughout the study. Propranolol had a significantly greater effect than sotalol in untreated dogs. The effects of both propranolol and sotalol were reduced by T3 ($P < 0.05$).

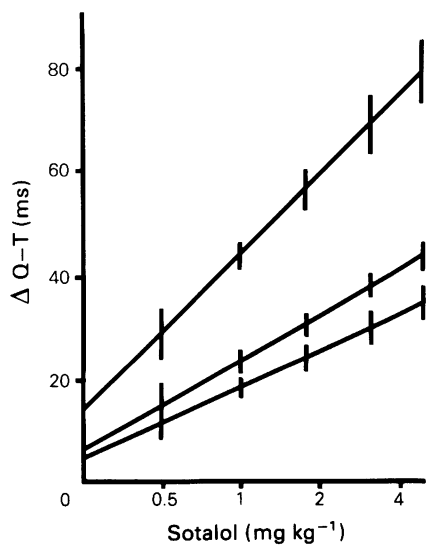

Figure 6 Regression lines of increments in Q–T interval on logarithm of dose of sotalol, during carbimazole-treated (lowest line), untreated (middle line) and T3-treated (uppermost line) states. The vertical bars represent 95% confidence limits. Each line is based on 64 observations in 4 dogs.

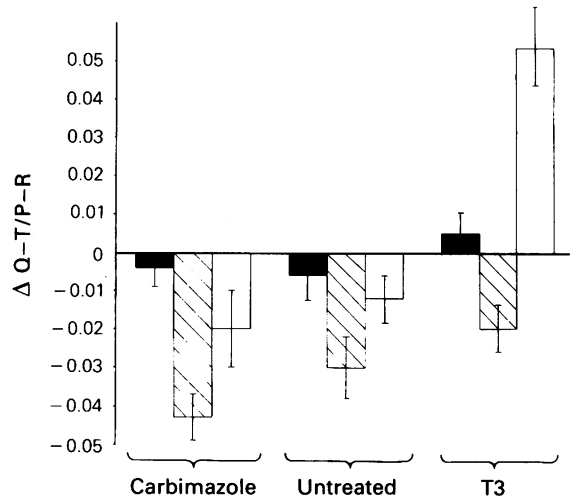

Figure 7 Mean changes in Q–T/R–R ratio evoked by the infusion of nadolol (solid columns), propranolol (hatched columns), and sotalol (open columns), all at doses giving IDR = 30. Results of duplicate experiments on 4 dogs untreated, during carbimazole treatment, and during T3 treatment. Vertical bars represent s.e.mean.

Actions on Q–T interval

Figure 5 shows the changes evoked by the same doses of the three antagonists, from the resting values shown in Table 1.

Nadolol again was without significant effect. Propranolol gave a small but significant ($P < 0.05$) prolongation, which was independent of thyroid state. Sotalol gave a substantial prolongation, which was dose-dependent over the range of doses studied, as is shown in Figure 6. This action of sotalol was significantly diminished by carbimazole treatment, and significantly enhanced by treatment with T3.

In Figure 7 the results for the three antagonists are replotted to show change in Q–T interval as a fraction of cycle duration. Propranolol reduced the fraction in all three thyroid states. Sotalol also reduced the fraction in the untreated and carbimazole-treated states, but increased it in the T3-treated state.

Actions of nadolol at high doses

Because of its lack of effect in the comparative study, nadolol was infused in two dogs up to 5 mg kg^{-1}. In the carbimazole-treated and untreated states no change in heart-rate was seen. In the T3-treated state, the heart rate was lowered by doses above 0.3 mg kg^{-1}. At a dose of 3 mg kg^{-1}, the mean reduction in heart-rate was 37 min^{-1}. At this dose the mean Q–T prolongation in carbimazole-treated, untreated and T3-treated states was 5, 15 and 26 ms respectively. No significant change in P–R interval was seen, in all three

thyroid states. Extrapolation from isoprenaline responses with lower doses of nadolol predicts an IDR for this dose of about 10^4. In practice, antagonism at $3\,mg\,kg^{-1}$ is unsurmountable.

Discussion

Accurate comparisons of the potencies of β-adrenoceptor antagonists are usually based on the measurement of their affinity constants on isolated preparations. On this basis propranolol and nadolol are of the same order of potency (Lee *et al.*, 1975). Our results agree with previous reports that *in vivo* the relative potency of nadolol, in comparison with propranolol, is substantially enhanced (Lee *et al.*, 1975; 1978).

We have shown that propranolol, sotalol and nadolol, given in doses at which they are equipotent as β-adrenoceptor antagonists, differ widely in their effects on heart-rate and particularly in their ability to control the tachycardia of experimental hyperthyroidism.

The lack of an effect of nadolol on heart-rate makes it impossible to attribute the actions of the other drugs to β-adrenoceptor antagonism. The effects of propranolol on heart rate, in line with its prolongation of the P–R interval, could be due to its Class I action on sodium channels (Vaughan Williams, 1970). The effects of sotalol on heart rate and on Q–T interval can be attributed to its Class III action on repolarization (Vaughan Williams, 1970). Although Q–T interval is not an absolute measure of action potential duration, since it is also affected by the synchrony of ventricular activation, it has been found to be a fair indication of the Class III action of drugs for which action potentials have been directly measured (Vaughan Williams, 1982). Furthermore, the actions of sotalol on both heart-rate and Q–T interval vary in a similar way with thyroid state.

Taggart *et al.* (1984), working on open-chested anaesthetized dogs, obtained equal degrees of prolongation of cardiac action potential duration with sotalol and nadolol, and our results seem at first sight to conflict with theirs. At their dosage of the drugs, however, we would predict that nadolol was 22 times as potent a β-adrenoceptor antagonist as sotalol. Our results with high doses of nadolol, although too scanty for statistical analysis, support a Class III action, but only in association with a much higher degree of β block. At low doses nadolol behaves as a very specific β-adrenoceptor antagonist.

The interactions between drugs and thyroid hormones implied by our results are interesting. They suggest that thyroid hormones potentiate the Class III action but inhibit the Class I action. The inference, a further reason for expecting Class III drugs to be specifically effective as antiarrhythmic agents in thyrotoxicosis, seems to deserve clinical investigation.

A physiological implication of our results is to invalidate arguments based specifically on the action of propranolol in favour of a sympathetic component in the tachycardia of hyperthyroidism. Beta antagonism alone had virtually no effect on heart-rate. Nevertheless, propranolol is more effective clinically in hyperthyroidism than our results would predict, even allowing for its Class I action (Shanks *et al.*, 1969). This could be due to a species difference between dog and man, or to long term actions of propranolol that would not have affected our results, such as inhibition of the conversion of T4 to T3 (Heyma *et al.*, 1980).

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